REMARKS

The Office Action mailed on August 02, 2006 has been received and its contents carefully considered.

The present Amendment revises claims 1, 4, 6, 8-12, 15, 18, 19, 21, 24, 26-30, 33, 36 and 37. Claims 1-38 are pending in the application. Claims 1 and 21 are the independent claims. The present Amendment also revises several passages in the specification.

At the top of page 2, the Office Action comments that claims 10 and 11 are the same as claims 28 and 29, respectively, and that one of each duplicate should be cancelled. Claims 10 and 11 depend (indirectly) from claim 1, and thus include the limitations of their predecessor claims. Similarly, claims 28 and 29 depend (indirectly) from claim 21. The different limitations in the chains of claims culminating in claims 10 and 11, on the one hand, and in claims 28 and 29, on the other hand, distinguish claims 10 and 11 from claims 28 and 29.

In section 1, the Office Action objects to claims 4, 6, and 24 under 37 CFR 1.75(c). Claims 4, 6, and 24 have been amended, by canceling didecanoyl phosphatidyl choline、dinonanoyl phosphatidyl choline, diarachidoyl phosphatidyl ethanolamine, dipalmitoleoyl phosphatidyl choline, dipalmitelaidoyl phosphatidyl ethanolamine. Also, the phase transition temperature T_{g1} of the first phospholipid in the independent claims has been amended into the range of 40 and 74 °C, and this amendment contains no new matter since MPEG (representing mPEG2000-DSPE) and distearoyl phosphatidyl ethanolamine (DSPE) have been used in the examples of the present invention. The transition temperature of "mPEG2000-DSPE" is 74 °C, which is the same as that of "DSPE." Thus,

claims 4, 6 and 24 have been placed in proper dependent form, and the objection is no longer applicable. It is requested that this objection be withdrawn.

In section 3, the Office Action rejects claims 8-18, 21 and 26-37 under the second paragraph of U.S.C. 112, and in section 5, the Office Action rejects claim 37 on similar grounds. The Office Action comments generally that a substance and/or "a derivative thereof" lead to a plethora of compounds, making the scope of the rejected claims unclear. Applicants respectfully disagree with this conclusion. Just because claim language is broad does not mean that it is indefinite. Despite this traverse, though, the present Amendment deletes the "derivative thereof" language from some (but not all) of the rejected claims. In others of the rejected claims, the derivatives have been limited to groups consisting of well-known compounds. The well-known derivatives of paclitaxel includes docetaxel; the well-known derivatives of retinoic acid include retinol, retinyl acylate and retinyl acetate; and the well-known derivatives of camptothecin include irinotecan, topotecan, SN-38, 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, 7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin, 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy-20(S)-camptothecin and 7-(2-N-isopropylamino)ethyl)-(20S)-camptothecin. Also, the well-known cholesterol derivatives include polyethylene glycol 600 mono(cholesteryl) ether sebacate and cholesteryl oleyl carbonate. Accordingly, it is respectfully submitted that the metes and bounds of the rejected claims are adequately clear, and that this rejection should be withdrawn.

The present Amendment also corrects the preamble of claim 21 in response to the rejection in section 4 of the Office Action.

Section 7 of the Office Action rejects claims 8-18 and 26-36 for non-enablement under the first paragraph of 35 USC 112. The Office Action generally takes the position that the "derivative thereof" language in the rejected claims makes them broader than the disclosure supports. It must be kept in mind, of course, that an ordinarily skilled person in any art must be fairly knowledgeable about that art in order to qualify as being ordinarily skilled. It is respectfully submitted that, in view of the claim amendments mentioned above and the knowledge of the art that an ordinarily skilled person would bring with him when he read the present disclosure, the rejected claims as presently formulated are adequately supported by the disclosure.

Claims 1-3, 5-9, 18 and 19 have been rejected under 35 U.S.C. 102(b), in section 9 of the Office Action, as being anticipated by Sheih et al (Journal of Fermentation and Bioengineering, 1997). In section 10, claims 1-9, 18 and 19 have been rejected under 35 U.S.C. 102(b) as being anticipated by Straubinger et al (US 5,415,869). In section 11, claims 1-7, 19, 21-25 and 37 have been rejected under 35 U.S.C. 102(b) as being anticipated by Scotto et al (US 4,873,089). Furthermore, section 12 rejects claims 1-3, 5-9, 15, 16, 18 and 19 under 35 U.S.C. 102(b) as being anticipated by Castor et al (US 5,776,486).

Claims 1, 4, 6, 8-12, 15, 18, 19, 21, 24, 26-30, 33, 36 and 37 have been amended, and it is submitted that amended independent claims 1 and 21, as well as the claims 2-20 and 22-38 dependent therefrom, are patentably distinguishable over the cited references for at least the following reasons.

It is well settled that a reference may anticipate a claim within the purview of 35 U.S.C. § 102 only if all the features and all the relationships recited in the claim are taught by the reference structure either by clear disclosure or under the principle of inherency.

Amended independent claim 1 is directed to a formulated liposome for incorporating a high content of hydrophobic substances, comprising a first phospholipid, a second phospholipid, one or more hydrophobic substances, and liposome-forming materials. The first phospholipid is selected from a hydrogenated naturally-occurring phospholipid or a saturated phospholipid with long carbon chains (-$(CH2)_n$-, the value of n is at least 14); and the second phospholipid is selected from an unsaturated phospholipid or a saturated phospholipid with short carbon chains (-$(CH2)_n$-, the value of n is at most 14). The first and the second phospholipids coexist in the liposome in two immiscible phases and create several discontinuous regions, and a molar ratio of the first phospholipid to the second phospholipid is larger than **1/20** (supported by paragraph [0043] in the specification and Tables 2, 3 and 4). Also, a phase transition temperature T_{g1} of the first phospholipid is in the range between 40 and 74 °C, and a phase transition temperature T_{g2} of the second phospholipid is in the range between –30 and 10 °C while a drug delivery temperature T_1 and a drug storage temperature T_2 are chosen at specified ranges subject to an order of $\mathbf{T_{g1} > T_1 > T_2 > T_{g2}}$.

Amended independent claim 21 is directed to a liposome for incorporating high content of hydrophobic substances comprising a first phosphatidyl choline, a second phosphatidyl choline, one or more hydrophobic substances, and liposome-forming materials. The first phosphatidyl choline is selected from a hydrogenated naturally-occurring phospholipid or a saturated phospholipid with long carbon chains (-$(CH2)_n$-, the value of n is at least 14); and the second phosphatidyl choline is selected from an unsaturated phospholipid or a saturated phospholipid with short carbon chains (-$(CH2)_n$-, the value of n is at most 14). The first and the second phosphatidyl cholines coexist in the liposome in two immiscible phases and create several discontinuous regions, and a molar

ratio of the first phosphatidyl choline to the second phosphatidyl choline is larger than 1/20. Also, a phase transition temperature T_{g1} of the first phosphatidyl choline is in the range between 40 and 74 °C, and a phase transition temperature T_{g2} of the second phosphatidyl choline is in the range between –30 and 10 °C, and a drug delivery temperature T_1 and a drug storage temperature T_2 are chosen at specified ranges subject to an order of $\mathbf{T_{g1} > T_1 > T_2 > T_{g2}}$.

First, the phase transition temperature T_{g1} of the first phospholipid in independent claims 1 and 21 has been amended into the range of 40 and 74 °C. This amendment contains no new matter since distearoyl phosphatidyl ethanolamine (DSPE) has been used in the examples of the present invention. Thus, the specification provides sufficient support for this phase transition temperature range of the first phospholipid.

The Office Action asserts that Sheih et al disclose "a formulation for lipsomes of egg phosphatidylcholine (EPC)/ dimyristoylphosphatidylglycerol (DMPG) in 7:3 molar ratio with 40% cholesterol, 25% α-tocopherol and **3% taxol** (paclitaxel)". In contrast to the present invention, the phase transition temperature of DMPG is about 25 °C, which is not within the range between 40 °C and 74 °C. Therefore, DMPG would not and could not be used as the first phospholipid in the sense of the present invention. Sheih et al does not disclose (or suggest) that the formulation for lipsomes comprises the first phospholipid having phase transition temperature of 40 °C to 74 °C and the second phospholipid having phase transition temperature of –30 °C and 10 °C. Besides, according to the formulation of Sheih, only 3% **taxol** (paclitaxel) is incorporated. However, the formulation of the claimed invention is able to incorporate 20 mole% paclitaxel, and the lipsomes remain stable (for example, at least 85% incorporation efficiency) for at least 60 days (please see paragraphs. [0037], [0039], [0058], and [0059], and Table 3). It is therefore respectfully

submitted that independent claim 1, and the claims 2-3, 5-9, 18 and 19 dependent therefrom, are patentably distinguishable (not anticipated and non-obvious) over the cited reference Sheih et al.

Straubinger et al (US 5,415,869) discloses a pharmaceutical formulation comprising one or more **negatively charged** phospholipids and one or more **zwitterions** phospholipids (please see claim 1, and examples 2-4 of columns 12 and 13). Straubinger's formulation remains physically stable for 75 days if it contains a very low content of taxol, such as no more than **2.1%** taxol (see Figure 5 and example 2). However, it is not necessary to use negatively charged and zwitterions phospholipids together in the claimed invention (for example, both of the first and second phospholipids could be negatively charged phospholipids or zwitterions phospholipids). According to the present application, the lipsomes are able to incorporate a very high content of paclitaxel, such as **20 mole%** paclitaxel, and remain stable for at least 60 days. The Straubinger et al reference does not disclose (or suggest) that the phase transition temperature (T_{g1}) of the first phospholipid (about 40 °C to 74 °C) is larger than the phase transition temperature (T_{g2}) of the second phospholipid (about –30 °C and 10 °C), and particularly does not disclose (or suggest) that a drug delivery temperature T_1 and a drug storage temperature T_2 are chosen at specified ranges such that $\mathbf{T_{g1} > T_1 > T_2 > T_{g2}}$. It is therefore submitted that independent claim 1, and the claims 2-9, 18 and 19 dependent therefrom, are patentably distinguishable (not anticipated and non-obvious) from the cited reference Straubinger et al.

The Scotto et al reference (US 4,873,089) discloses a process for the preparation of fusogenic proteolipsomes. Although some phospholipids have been mentioned in column 5, lines 37-64, Scotto et al doe not disclose (or suggest) that the formulation for lipsomes comprises the first and second phospholipids in accordance with the independent claims, or

the condition that the phase transition temperature (T_{g1}) of the first phospholipid (about 40 °C to 74 °C) is larger than the phase transition temperature (T_{g2}) of the second phospholipid (about –30 °C and 10 °C) in accordance with the independent claims. Besides, Scotto's formulation is used for incorporating proteins, and not used for incorporating hydrophobic substances. Accordingly, this reference nowhere shows or suggests a formulation incorporating a large amount (for example, at least 20 mole% paclitaxel) of hydrophobic substances, and in particular, the limitations concerning the phase transition temperatures of the first and second phospholipids. It is therefore respectfully submitted that independent claims 1 and 21, and the claims 2-7, 19, 22-25 and 37 dependent therefrom, are patentably distinguishable (not anticipated and non-obvious) from Scotto et al.

Castor et al (US 5,776,486) disclose phospholipid materials containing fresh chicken egg yolk and soy bean phosphatidylcholine, wherein the chicken egg yolk consisted of 60% phosphatidyl choline (PC) and 16.5% phosphatidyl ethanolamine (PE) (column 23, line 10-line 15). Egg yolk is an unpurified EPC, and both of PE and soy bean PC are unsaturated phospholipids. The Castor et al reference does not disclose (or suggest) that first and second phospholipids are required and restricted in the limitation that the phase transition temperature (T_{g1}) of the first phospholipid (about 40 °C to 74 °C) is larger than the phase transition temperature (T_{g2}) of the second phospholipid (about –30 °C and 10 °C). Also, the Castor et al reference does not disclose (or suggest) that a drug delivery temperature T_1 and a drug storage temperature T_2 are chosen at specified ranges such that $\underline{T_{g1} > T_1 > T_2 > T_{g2}}$. As such, it is submitted that independent claim 1, and the claims 2-3, 5-9, 15, 16, 18 and 19 dependent therefrom, are patentably distinguishable (not anticipated and non-obvious) over the cited reference Castor et al.

According to the reasons presented above, it is respectively requested that the rejections under 35 U.S.C 102(b) be withdrawn.

Sections 16 and 17 of the Office Action reject claims 20 and 38 under 35 USC 103(a) as being unpatentable over Scotto et al (US 4,873,089) in view of Crosasso et al, and reject claims 1-19 and 21-37 under 35 U.S.C. 103(a) as being unpatentable over Scotto et al (US 4,873,089) in view of Unger et al (US 5,733,572) and Castor et al (US 5,776,486). Independent claims 1 and 21 have been amended. It is submitted that these claims are now *prima facie* patentably distinguishable over this reference for at least the following reasons.

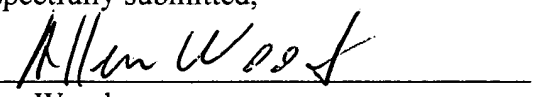
It is well-settled law that in order to properly support an obviousness rejection under 35 USC 103, there must have been some teaching in the prior art to suggest to one skilled in the art that the claimed invention would have been obvious. *W. L. Gore & Associates, Inc. v. Garlock Thomas, Inc.*, 721 F.2d 1540, 1551 (Fed. Cir. 1983).

None of the cited references, including Scotto et al (US 4,873,089), Crosasso et al, Unger et al (US 5,733,572), and Castor et al (US 5,776,486), teach or suggest the lipsome formulations defined in the independent claims, such as the limitation that the phase transition temperature (T_{g1}) of the first phospholipid is larger than the phase transition temperature (T_{g2}) of the second phospholipid, and the limitation that a drug delivery temperature T_1 and a drug storage temperature T_2 are chosen at specified ranges subject to $T_{g1} > T_1 > T_2 > T_{g2}$. Those limitations are the key features for incorporating high contents hydrophobic substances in the lipsomes, and the storage stability of the lipsome formulation is greatly improved (please see Table 3). Those features are beyond the teachings of the cited references, and the advantages cannot be achieved by combining the disclosures in the cited references. Hindsight cannot be used to arrive at a determination of

obviousness. It has been stated that one cannot use hindsight reconstruction to pick or choose among isolated disclosures in the prior art to deprecate the claimed invention (*In re* Fine, 837 F.2d 1071, 1075, 5USPQ2d 1596, 1600 (Fed. Cir. 1988)). Thus, it is submitted that it would not have been obvious to a person ordinarily skilled in the art to make such a combination.

Accordingly, it is submitted that the amended independent claims 1 and 21 are patentably distinguishable over the prior art, and claims 2-20 and 22-38 are allowable for at least the reason that they depend from claims 1 and 21, so that this application is in condition for allowance. Allowance of the application and the passing of this case to issue are therefore respectfully requested.

Respectfully submitted,



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